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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,523	03/23/2004	Nnochiri N. Ekwuribe	9233-64CT	2734

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EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,523	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050314;20040323*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-104 of U.S. Patent No. 6,713,452. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '452 patent clearly anticipate the instant claims.

3. Claims 19 and 20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of U.S. Patent No. 6,815,802 in view of Lee et al (U.S. Patent No. 6,506,730). Although the conflicting claims are not identical, they are not patentably distinct from each other. The '802 patent claims the same method steps as are recited in the instant claims for forming the substantially monodispersed mixture of polymers having the structure of Formula III, but does not claim then activating the polymers and reacting them with calcitonin in order to form calcitonin conjugates. Lee et al teach forming PEG-calcitonin conjugates by first activating the PEG with N-hydroxysuccinimide and then reacting the activated PEG with the calcitonin (see, e.g., column 5, lines 61-67, and Example 1). It would have been obvious to one of ordinary skill in the art to use the claimed method of the '802 patent as a source of the PEG used in Lee et al's method to form PEG-calcitonin conjugates because it

is prima facie obvious to use the product of one process as the source of reactant for another process (see In re Kamlet, 88 USPQ 106 (CCPA 1950)).

4. Claims 1-6 and 8-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-130 of U.S. Patent No. 6,770,625. Although the conflicting claims are not identical, they are not patentably distinct from each other. The '625 claims specific conjugates in which an oligomer comprising a polyethylene glycol moiety is conjugated to an amine function of calcitonin (see, e.g., claims 18, 39, 57, 80, 102, and 122), and claims the use of calcitonin-oligomer conjugates which are present as monodispersed mixtures (see, e.g., claims 20, 41, 59, 82, 104, and 124), but does not claim the specific conjugates in monodispersed form. It would have been obvious to one of ordinary skill in the art to formulate and use the specific claimed conjugates of the '625 patent in monodispersed form also claimed by the '625 patent because the use of homogeneous and uniform compositions in the therapeutic arts is preferred for purposes of predictability and reduced side effects, and because it is prima facie obvious to operate according to the most preferred and claimed embodiments of the '625 patent. Because the specific conjugates claimed by the '625 patent have the same structure claimed by Applicants, inherently the former will be capable of lowering serum calcium levels by at least 5 percent, will have an increased resistance to degradation by chymotrypsin or trypsin in comparison to unconjugated calcitonin, and will have a greater bioefficacy in comparison to unconjugated to calcitonin, to the same extent as is claimed by Applicants. With respect to instant claim 14, while the '625 patent claims treating bone disorders with its conjugates, it does not claim treating osteoporosis, Paget's disease, or hypercalcemia in particular. It would have been obvious to one of ordinary skill in the art to

treat osteoporosis, Paget's disease, or hypercalcemia using the monodisperse calcitonin-oligomer conjugates suggested by the claims of the '62 patent because calcitonin is most commonly used to treat osteoporosis, Paget's disease, and hypercalcemia, and because calcitonin in conjugated form would have been expected to be useful in treating the same types of bone disorders which are treated using unconjugated calcitonin.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

6. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being obvious over the European

Patent Application 0 511 903 in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. The European Patent Application '903 teaches polyethylene glycol having a molecular weight of 500-20,000 conjugated to the carboxylic group of human, salmon, or eel calcitonin via formation of an amide bond. The conjugates are used to treat osteoporosis, hypercalcaemia, and Paget's disease. See, e.g., the Abstract. While the European Patent Application '903 does not teach the degree to which the conjugates are able to lower serum calcium levels, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, in order to maximize its conjugates' desirable properties. While the European Patent Application '903 does not teach that conjugation increases resistance to chymotrypsin degradation and increases bioefficacy, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made that the conjugation of the European Patent Application '903 would have these results because it is well-known in the art, as shown by the WO Patent Application '740 at page 2, lines 3-13, that PEG conjugation to proteins decreases in vivo proteolysis and increases in vivo half-lives of the proteins compared to their unconjugated state. The European Patent Application '903 does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which

have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-calcitonin conjugates of the European Patent Application '903 using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by the European Patent Application '903; because the use of discrete length PEG in the conjugates of the European Patent Application '903 would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

7. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application 0 511 903 in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740 as applied against claims 15-17 above, and further in view of the Harris et al article (J. Macromol., Sci., Vol. C25, pages 325-373). As noted above, while the European Patent Application '903 does not teach degree to which the conjugate is able to lower serum calcium levels, the Harris et al article teaches that when using PEG-protein conjugates, the degree of substitution and PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to

optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, as taught by the Harris et al article for the PEG-calcitonin conjugates of the European Patent Application '740 in order to maximize the conjugate's desirable properties.

8. Claims 15-18 are rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Ekwuribe teaches conjugates in which a polymer comprising a PEG moiety which preferably has more than 7 subunits and a lipophilic moiety is conjugated via a labile bond to a peptide, which can be calcitonin and which conjugation can occur at an amine group present on the peptide. Plural polymers can be conjugated to each peptide. Conjugation results in prolonged blood circulation and enhanced resistance to enzymatic degradation, relative to the peptide alone. See, e.g., the Abstract; column 6, lines 49-61; column 11, lines 19-20; column 12, lines 11-16 and 35-40; column 13, Conjugates 2 and 3; and column 14, lines 3-14 and 43-55. While Ekwuribe does not teach the degree to which calcitonin conjugates are able to lower serum calcium levels, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, in order to maximize its conjugates' desirable properties. While Ekwuribe does not teach using calcitonin-based conjugates to treat bone disorders such as osteoporosis, Paget's disease, or hypercalcaemia, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the calcitonin-based conjugates of Ekwuribe to treat such bone disorders because the treatment of such bone disorders is one of the primary uses of calcitonin. Ekwuribe does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado

et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application 97/14740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the calcitonin conjugates of Ekwuribe using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Ekwuribe; because the use of discrete length PEG in the conjugates of Ekwuribe would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

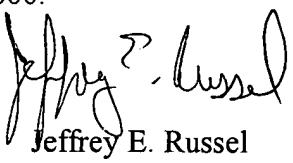
9. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740 as applied against claims 15-18 above, and further in view of the Harris et al article (J. Macromol., Sci., Vol. C25, pages 325-373), the European Patent Application 0 511 903, or Lee et al (U.S. Patent No. 6,506,730). As noted above, while Ekwuribe does not teach

degree to which the conjugate is able to lower serum calcium levels, the Harris et al article teaches that when using PEG-protein conjugates, the degree of substitution and PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, as taught by the Harris et al article for the PEG-calcitonin conjugates of Ekwuribe in order to maximize the conjugate's desirable properties. As noted above, Ekwuribe does not teach using calcitonin-based conjugates to treat bone disorders such as osteoporosis, Paget's disease, or hypercalcaemia. The European Patent Application '903 teaches polyethylene glycol conjugated to human, salmon, or eel calcitonin and used to treat osteoporosis, hypercalcaemia, and Paget's disease. See, e.g., the Abstract. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the calcitonin-based conjugates of Ekwuribe to treat such bone disorders because the treatment of such bone disorders is one of the primary uses of calcitonin conjugates as shown by the European Patent Application '903. See, e.g., the Abstract. Ekwuribe does not teach using salmon calcitonin as the source of the calcitonin for its conjugates, and does not teach conjugation at the Lys^{11} or Lys^{18} residue of the salmon calcitonin. Lee et al teach salmon and eel calcitonins have the most effect as the source of calcitonin in PEG-calcitonin conjugates used to treat hypercalcemia, Paget's disease, and osteoporosis, and teach conjugation through the N-terminus, the Lys^{11} residue, or the Lys^{18} residue of the calcitonin. See, e.g., column 6, lines 23-30, and claim 2. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use salmon calcitonin as the source of the calcitonin for the conjugates of

Ekwuribe because Lee et al teach that salmon calcitonin is an effective source of calcitonin in making such conjugates and because salmon calcitonin possesses therapeutic properties which would have been expected to have been useful in the conjugates of Ekwuribe. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to conjugate the polymers of Ekwuribe to the sidechains of either of the Lys residues present in salmon calcitonin because Lee et al disclose that these residues are useful attachment points for forming calcitonin conjugates.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

June 17, 2005